Comparing clinical rating scales in genetic FTD within the GENFI cohort

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Background

The heterogeneity of frontotemporal dementia (FTD) presents a challenge for determining reliable outcome measures for therapeutic interventions. This study proposes a new scale – the GENFI Clinical Rating Scale (GENFI-CRS) – which aims to be more sensitive, detect changes within the presymptomatic group and reduce sample sizes needed for clinical trials.

Methods

Subjects were recruited as part of the GENetic Frontotemporal dementia Initiative (GENFI). A total of 685 individuals were included in the cross-sectional analysis: 263 gene negative controls, 293 presymptomatic gene carriers and 129 symptomatic individuals (*Table 1*). 189 individuals also had a yearly follow up visit (20 symptomatic carriers and 169 presymptomatic carriers). Presymptomatic carriers were categorised as 'early' or 'late' based on their years from estimated onset (early: >10.0 years from estimated onset; late: <10.0 years)

	Gene negative control	Presymptomatic carrier	Symptomatic carrier	Total
C9orf72	-	107	63	**170**
GRN	-	134	43	**177**
MAPT	-	52	21	**73**
Total	**263**	**293**	**127**	

Table 1. Participant demographics

Participants underwent a standardised assessment at baseline and follow up. This included a clinical assessment with a semi-structured interview of both the participant and carer. The clinical assessment encompassed the Clinical Dementia Rating scale (CDR), the Frontotemporal Lobar Degeneration Clinical Dementia Rating Scale (FTLD-CDR), GENFI Clinical Rating Scale (GENFI-CRS), Cambridge Behavioural Inventory – Revised (CBI) and Frontotemporal Dementia Rating scale (FRS). Clinicians assessed CDR, FTLD-CDR and GENFI-CRS symptom severity as 0, 0.5, 1, 2 or 3 where 0 is no symptoms and 3 is severe symptoms. Sum of boxes scores were then computed. The CBI and FRS were completed by an informant close to the participant. The GENFI-CRS is a 10 item scale, based on the 8 items of the FTLD-CDR with the addition of neuropsychiatric and motor scores to address the comorbidity of FTD and motor neurone disease and the neuropsychiatric presentations seen with the *C9orf72* expansion. A mixed effect model compared performance on each scale between genetic status groups. As the data was not normally distributed, bootstrapping was used for inference.

Results

The symptomatic carriers scored significantly higher on all scales than all other groups. There was also a marginally significant difference between early and late presymptomatic carriers in the GENFI-CRS, CDR and FTLD-CDR (late > early). Scores for early and late presymptomatic carriers were moderately higher for the GENFI-CRS compared to the CDR and FTLD-CDR.

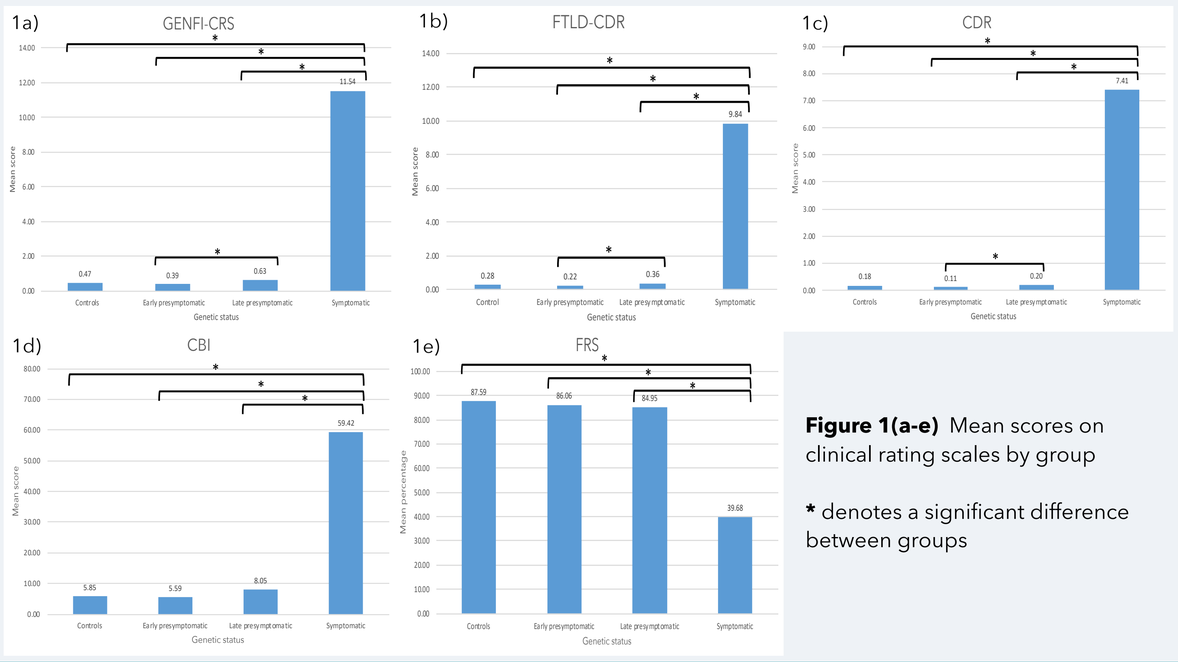

Figure 1(a-e) Mean scores on clinical rating scales by group

***** denotes a significant difference between groups

Results

Sample size calculations

Sample sizes are shown below per arm for a 1:1 randomised controlled trial to have 80% power at 5% significance level to detect a treatment effect over 1 year duration for each genetic status, mutation and time to estimated onset.

	Group	Mean Change	Rho	50% treatment effect	25% treatment effect
GENFI-CRS	All Symptomatic	4.41	0.76	69	274
CDR	All Symptomatic	3.38	0.71	75	301
FTLD-CDR	All Symptomatic	4.06	0.75	67	267
CBI	All Symptomatic	11.02	0.84	227	908
FRS	All Symptomatic	-7.35	0.83	324	1296
GENFI-CRS	*C9orf72*	5.05	0.76	39	155
CDR	*C9orf72*	4.21	0.66	41	163
FTLD-CDR	*C9orf72*	4.79	0.74	41	164
CBI	*C9orf72*	10.27	0.74	303	1214
FRS	*C9orf72*	-4.17	0.87	460	1841
GENFI-CRS	*GRN*	5.07	0.77	52	206
CDR	*GRN*	3.73	0.74	62	247
FTLD-CDR	*GRN*	4.55	0.77	49	197
CBI	*GRN*	14.98	0.85	137	548
FRS	*GRN*	-12.24	0.72	228	913
GENFI-CRS	*MAPT*	1.90	0.78	548	2193
CDR	*MAPT*	0.98	0.79	1007	4027
FTLD-CDR	*MAPT*	1.65	0.79	536	2144
CBI	*MAPT*	4.78	0.95	561	2244
FRS	*MAPT*	-4.63	0.96	258	1031

Table 2. Estimated sample sizes for a trial in symptomatic individuals

For all symptomatic individuals, the GENFI-CRS and FTLD-CDR gave rise to lower sample sizes in comparison to the other scales. When grouped by mutation type, the GENFI-CRS was lowest for *C9orf72* carriers and the FTLD-CDR for *GRN* carriers. However, the GENFI-CRS, CDR and FTLD-CDR resulted in relatively similar sample sizes for both *C9orf72* and *GRN* carriers. The *MAPT* group resulted in much larger sample sizes for all scales compared to the other mutations, with the FRS resulting in the lowest sample.

	Group	Mean Change	Rho	50% treatment effect	25% treatment effect
GENFI-CRS	EARLY	0.05	0.70	5014	20054
CDR	EARLY	0.03	0.78	3822	15287
FTLD-CDR	EARLY	0.00	0.68	804060	3216241
CBI	EARLY	0.41	0.66	13479	53918
FRS	EARLY	-2.61	0.27	3171	12682
GENFI-CRS	LATE	0.44	0.20	852	3406
CDR	LATE	0.21	0.15	1124	4495
FTLD-CDR	LATE	0.33	0.13	1000	3999
CBI	LATE	2.16	0.61	1093	4372
FRS	LATE	-2.39	0.55	1312	5250

Table 3. Estimated sample sizes for a trial in presymptomatic individuals

Sample sizes were also calculated for the early and late presymptomatic groups. Sample sizes were lower for the GENFI-CRS in the late presymptomatic group, however sample sizes for both early and late groups were large.

Conclusion

The GENFI-CRS and FTLD-CDR resulted in lower sample sizes for symptomatic individuals, in particular when grouped by mutation type. However, the sample sizes generated for MAPT symptomatic carriers were considerably larger with the lowest sample size resulting from the FRS. This could be due to a slower rate of progression within MAPT carriers. This has clear implications for determining outcome measures in clinical trials. Mixed effect modelling revealed significant differences between the early and late presymptomatic groups, suggesting increased sensitivity to change happening prior to symptom onset, using the GENFI-CRS, FTLD-CDR and CDR scales. Detecting the subtle changes that happen prior to onset of symptoms is important for future clinical trials in presymptomatic individuals. Sample sizes were lower for the GENFI-CRS in the late presymptomatic group, suggesting that it is a more sensitive measure for the changes in this period. However all sample sizes were too large to be feasible in practice as outcome measures for clinical trials. Overall, as the GENFI-CRS detected differences within presymptomatic individuals and resulted in relatively low sample sizes in the symptomatic group, it may prove useful as an outcome measure for future clinical trials.

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